



To Understand, Prevent and Heal the Effects of Stress

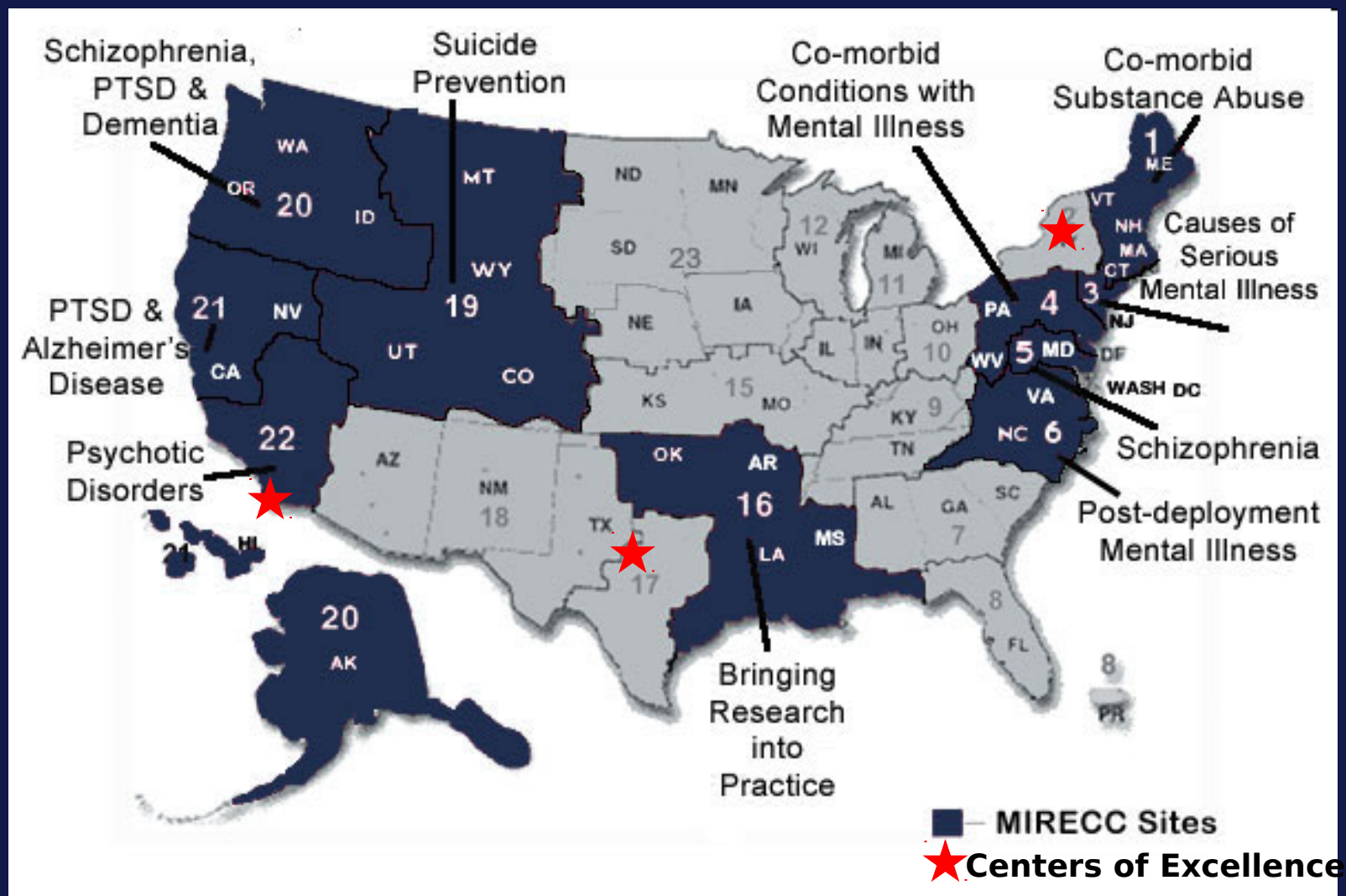
James Lohr, M.D. - Director

**Laurie Lindamer, Ph.D. - Director of
Education**

Dewleen Baker, M.D. - Director of Research

Niloo Afari, Ph.D. - Director of Clinical

MIRECCs and COEs



CESAMH Vision

Through clinical and translational research, innovative therapeutic programs, and education and training, to be a national resource for cutting-edge understanding and state-of-the-art treatment of stress- and trauma-related problems.



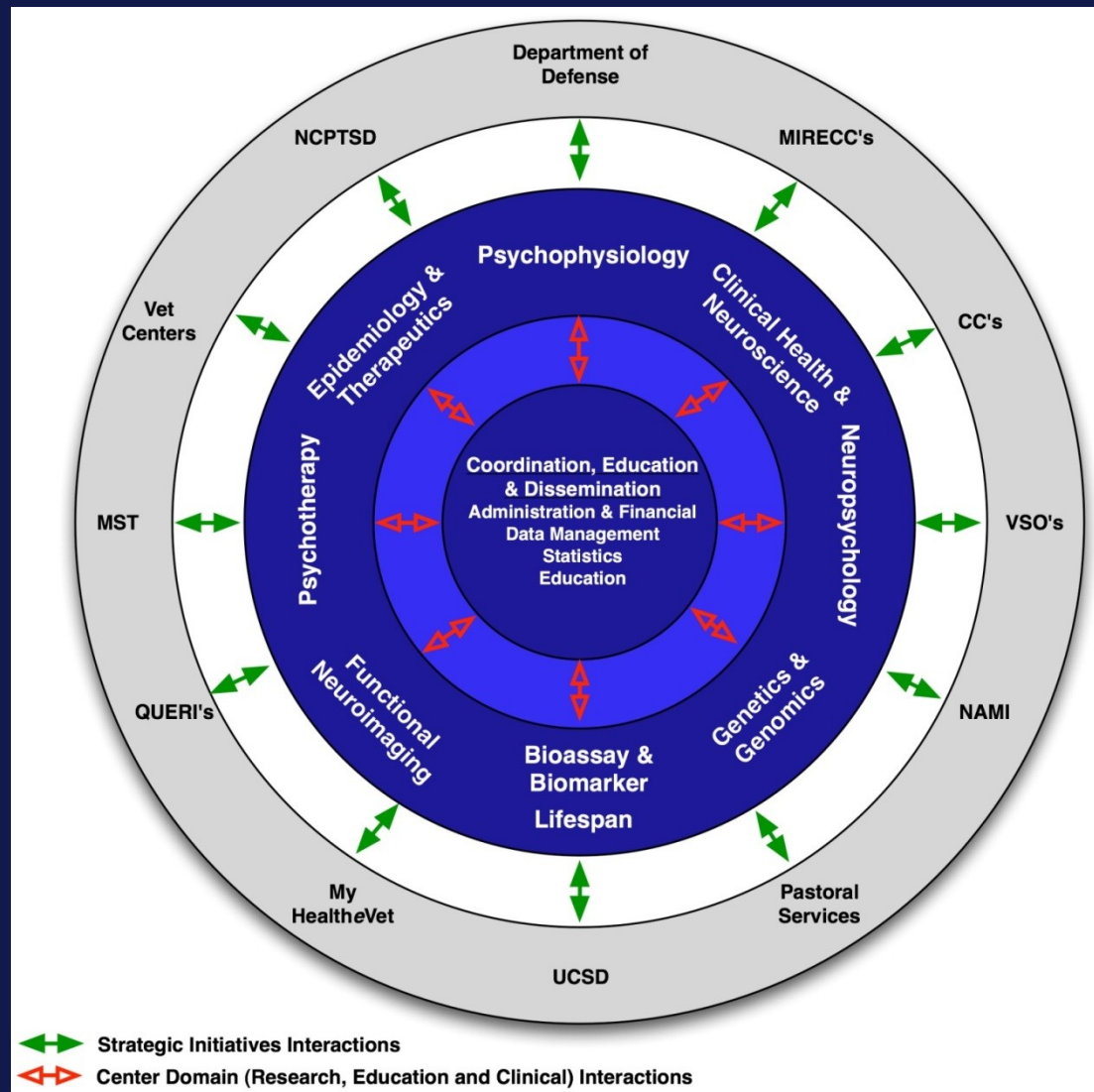
Center Focus

- ◆ **The effects of stress in the Operation Iraqi Freedom (OIF)/ Operation Enduring Freedom (OEF) contingents and veterans.**
- ◆ **Post-traumatic stress disorder (PTSD).**
- ◆ **The mental health concomitants of traumatic brain injury (TBI).**
- ◆ **The interaction of physical and mental health consequences of stress exposure.**

Functional Units

- ◆ **Coordination, Education, and Dissemination Unit (J. Lohr, L. Lindamer, C. Rodgers and M. Frybarger)**
- ◆ **Clinical Health and Neuroscience Unit (D. Baker, N. Afari and T. Moeller-Bertram)**
- ◆ **Epidemiology, Genomics and Therapeutics Unit (J. Lohr, M. Tsuang and C. Nievergelt)**
- ◆ **Functional Neuroimaging Unit (M. Paulus and A. Simmons)**
- ◆ **Stress and Pain Unit (I. Strigo and T. Moeller-Bertram)**
- ◆ **Lifespan Unit (W. Kremen and S. Ancoli-Israel)**
- ◆ **Neuropsychology Unit (D. Delis, A. Jak and B. Twamley)**
- ◆ **Psychophysiology Unit (V. Risbrough and M. Geyer)**
- ◆ **Psychotherapy Unit (A. Lang, S. Thorp and S. Norman)**
- ◆ **Bioassay and Biomarker Unit (R. Kuczenski and R. Hauger)**

CESAMH Collaboration



Clinical Activities

- **Planned development of the Women's Combat PTSD program (with Naval Medical Center San Diego)**
- **VISN-22 Clinical Assessment for Reintegration and Enrollment (CARE) in Veterans Transition Centers**
- **Peritraumatic Behavior Questionnaire for assessment of embedded personnel (in collaboration with DOD (W. Nash, Navy & Marine Corps))**

Education Activities

◆ Training in Evidence-Based Practices

- VA, DoD, Vet Centers, Community Providers
- Prolonged Exposure Therapy (n=60)
- Cognitive Processing Therapy (>200)
- Implementation of CPT CE course

◆ Dissemination

- Publication in scientific journals
- National Newsletter
- Education for Probation and Police Departments about incarcerated veterans
- Educational seminars for veterans with TBI

◆ Collaboration and communication both within the CESAMH and other relevant agencies

- Community Advisory Board
- MIRECCs, other CoEs

Research in CESAMH

- ◆ CESAMH provides infrastructure for research studies
- ◆ CESAMH provides salary support for researchers
- ◆ CESAMH provides opportunities for interactions between CESAMH researchers and the DOD
- ◆ CESAMH provides for translational research collaborations

Collaborations with DOD

- ◆ **Funding through the new CDMRP mechanisms**

Other active research collaborations include

- **Naval Health Research Center**
- **Naval Center Combat and Operational Stress Control**
- **Marine Corps**
- **INTRUST (Army, Ft. Detrick)**

VISN-22 CESAMH: PTSD Research

Activities

Major Clinical Research Studies, collaborations with DOD

- **Marine Resiliency Study (Marines), funded by VAHSR&D, USMC, and Navy BUMED**
 - **This study evaluates two battalions of Marines pre- and post-deployment to determine genetic, physiological, and neuropsychological factors related to resiliency to the development of PTSD**
- **Validation of the Peritraumatic Behavior Questionnaire-Observer Rated, funded by CDMRP**
 - **The PBQ is an instrument for assessment of embedded personnel to assess in-theater risk for combat PTSD Marines**
- **Telemedicine for Evidence-Based Psychotherapies, funded by VA and by VA and CDMRP**
 - **These are studies of the use of telemedicine to deliver PE and CPT treatment for PTSD**
- **Pain Perception and PTSD, funded by FAER**
- **Alcohol Use Disorder and PTSD Treatment in Victims of Partner Violence, funded by NIH**
- **Using fMRI to Measure Brain Response to Exposure-Based Psychotherapy in Individuals with Combat-Related PTSD, funded by CDMRP**



VISN-22 CESAMH: PTSD Research Activities

We are a site for the following Multisite Studies

- **Nepicastat for PTSD, funded by CDMRP**
- **Ganaxone for PTSD, funded by the Consortium for Psychological Health and Traumatic Brain Injury (Injury, Stress, and Trauma, INTRUST)**
- **Multisite Study of CBT for PTSD, funded by Navy BUMED (in collaboration with the NCPTSD)**
- **VA Cooperative Study #519 Genetic Tissue Banking for Integrating Practice Guidelines for Smoking Cessation into Mental Health Care for PTSD (funded by the VA)**



VISN-22 CESAMH: PTSD Research Activities

Major Basic Studies into Stress Mechanisms

- **CRF-R1 ERK Signaling and Mediation of Stress and Startle Hyperreactivity, funded by VA**
- **Assessing Fear Extinction via Startle, funded by VA and CDMRP**
- **Understanding the Role of COMT Variants in Sensorimotor Gating, funded by NIH**
- **Understanding neurobiological mechanisms underlying Pain and PTSD, funded by FAER**

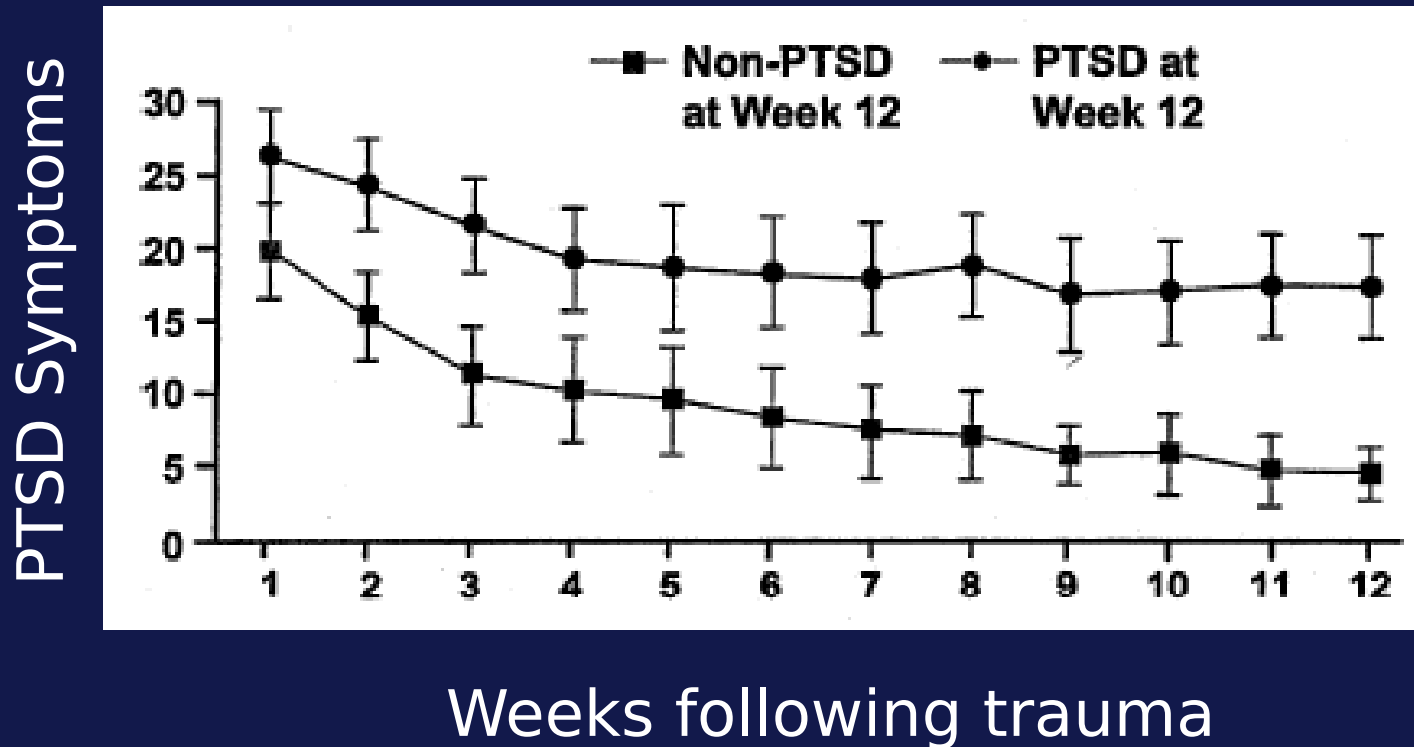
Examples of Translational Research in CESAMH

Corticotropin releasing factor in PTSD
Victoria Risbrough Ph.D.

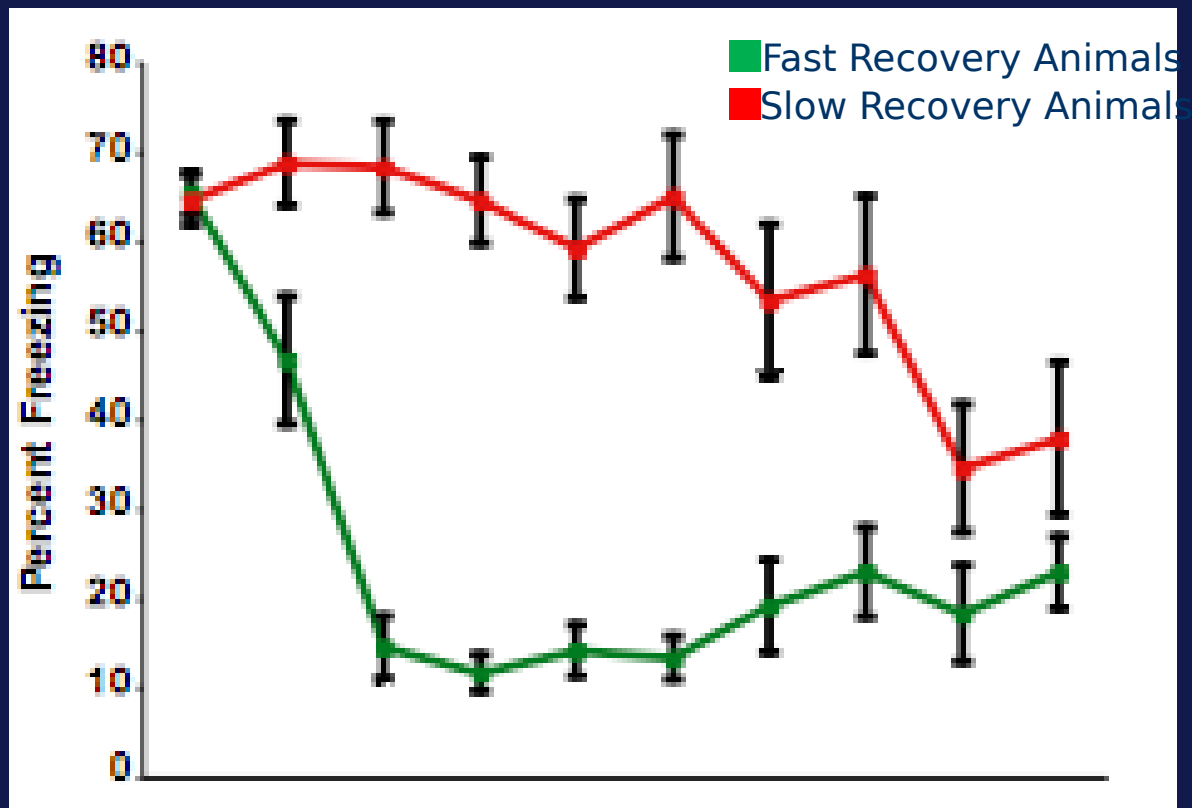
Neuropeptide Y in risk and resilience
for PTSD
Dewleen Baker M.D.



Extant hypothesis: PTSD is due to a failure in fear recovery mechanisms



Using a mouse model to test the hypothesis that individual variance in NPY signaling predicts fear recovery from trauma



→ Aim 1: Analysis of NPY expression and signaling pre and post trauma.

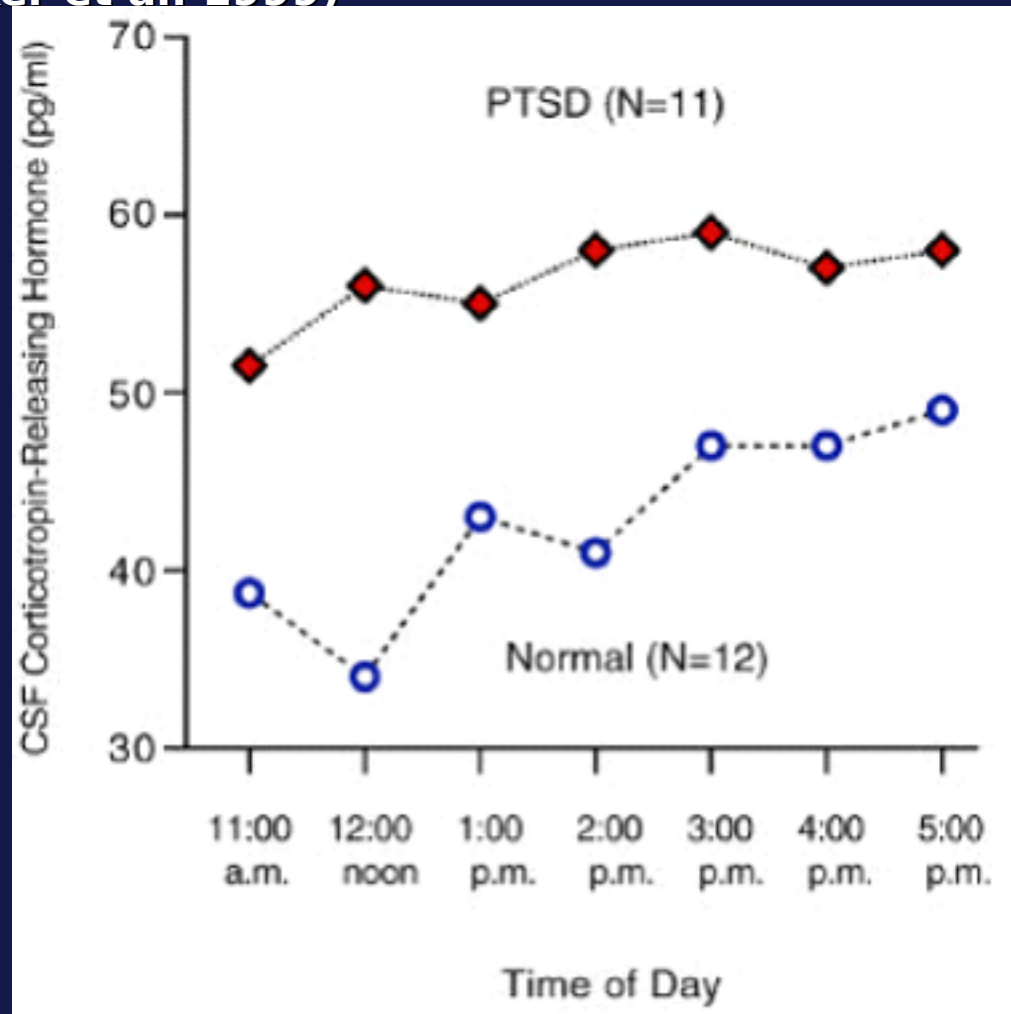
Aim 2: Does increasing NPY expression facilitate slow learner recovery?

Repeated Cue Exposure →

Corticotropin Releasing

Factor

- ◆ **Hypersecretion of CRF is exhibited in PTSD and depression** (e.g. Holsboer et al 1986, Nemeroff et al 1984, Bremner et al 1997, Baker et al. 1999)

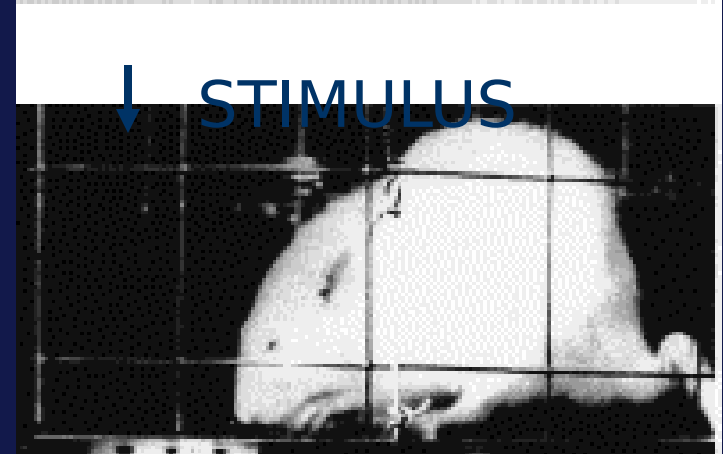
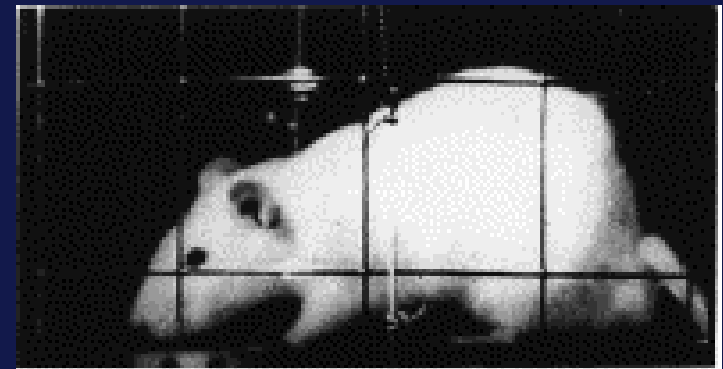
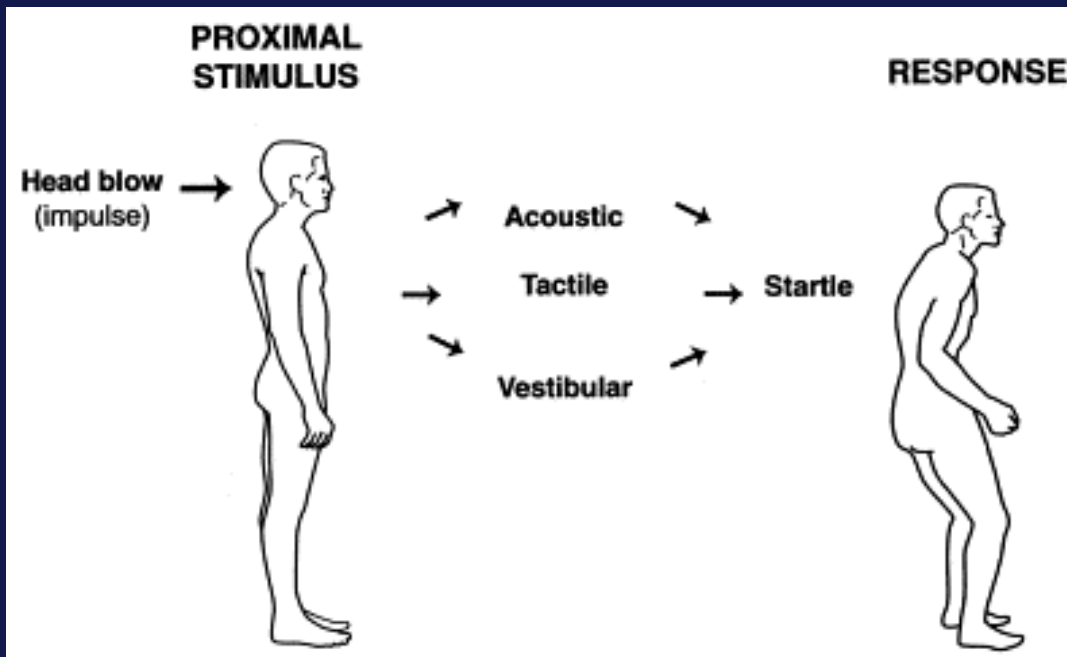


Broad Questions:

- ◆ Does CRF play a role in PTSD symptoms?
- ◆ Is increased CRF a vulnerability factor for development of PTSD or does it occur only after trauma exposure in PTSD subjects?
- ◆ What is the mechanism of CRF effects on stress responses?
- ◆ What are areas of potential efficacy for drugs targeting CRF - prophylactic or therapeutic?

Acoustic Startle Reflex

- Acoustic startle reflex: a contraction of the skeletal musculature in response to a high intensity acoustic stimulus.
- Postulated function: Defensive mechanism for protection from immediate attack.
- **Exaggerated startle a hallmark symptom of combat related PTSD**

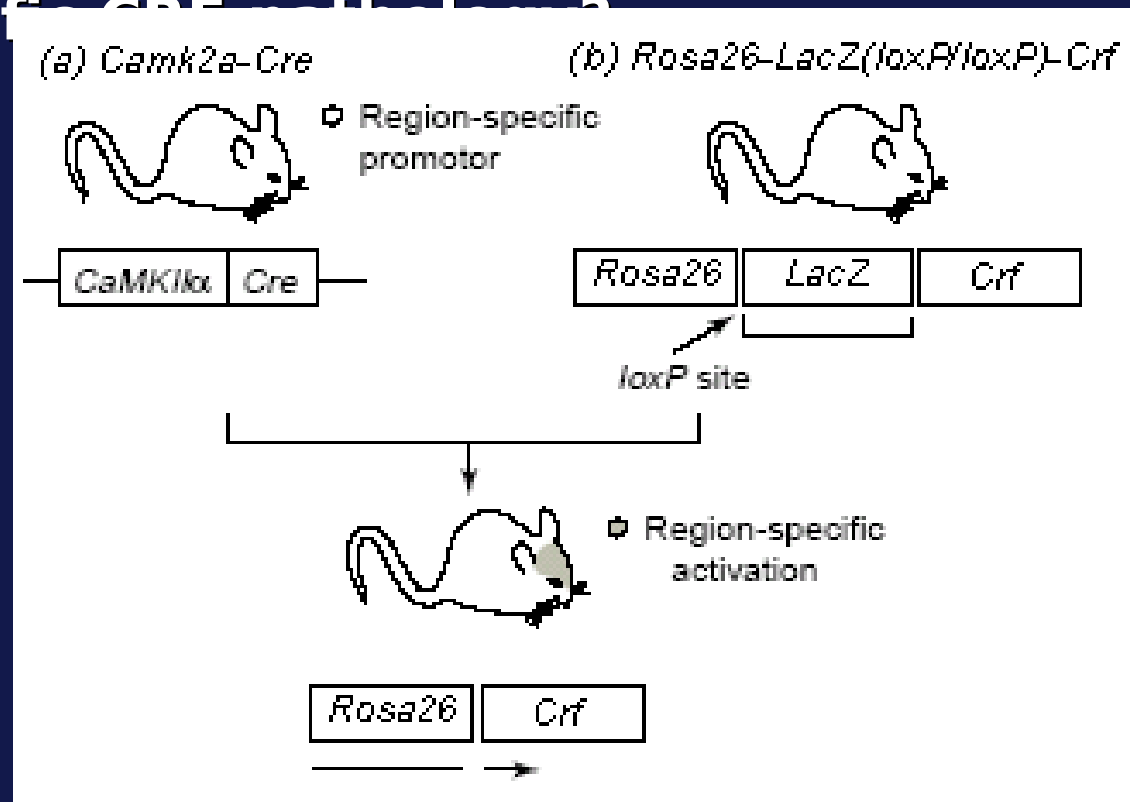


Yeomans et al. 2002

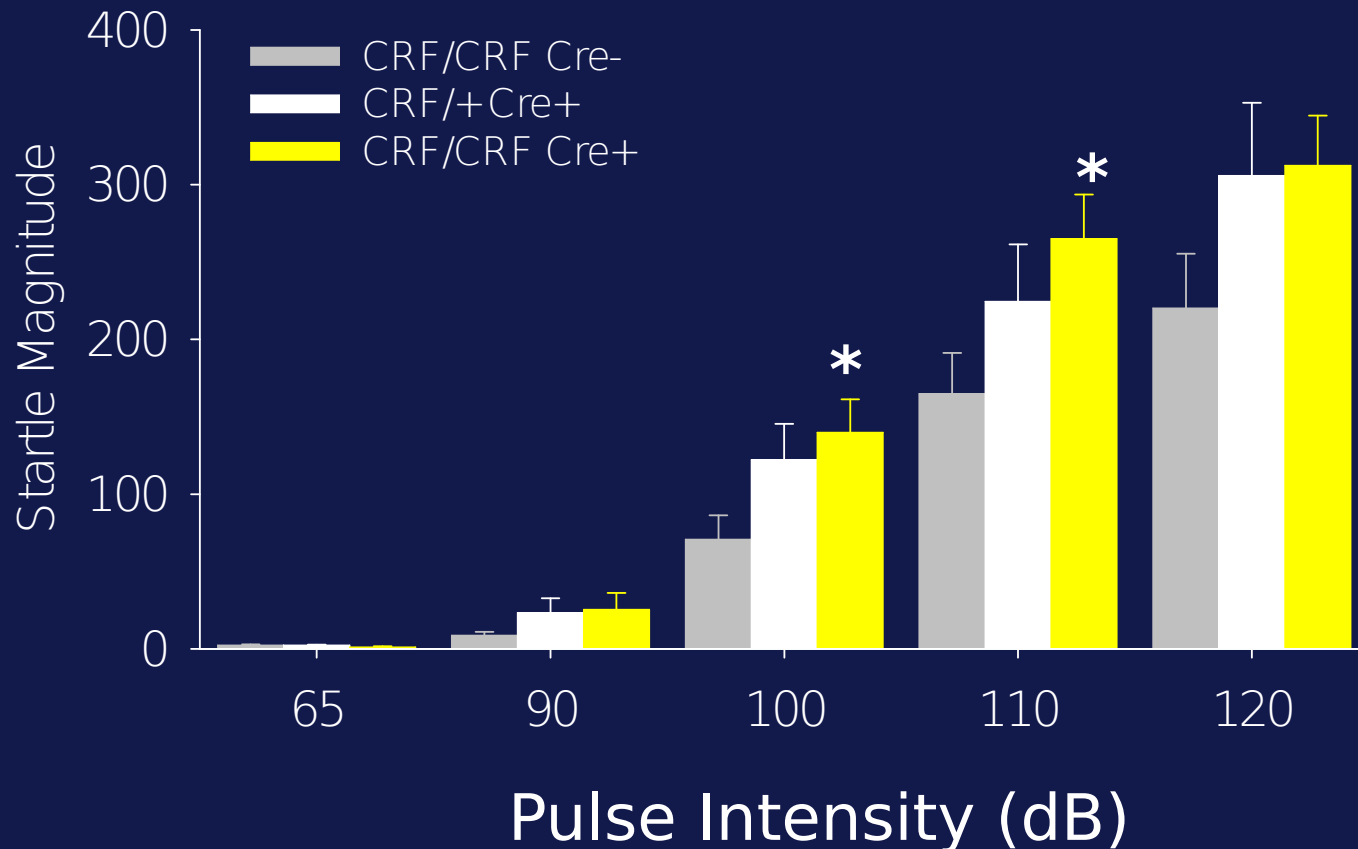
Adapted from Horlington 1970

Modeling chronic CRF effects on startle via targeted overexpression

- ◆ PTSD patients exhibit increased CRF concentrations in CSF (Baker et al 1999; Bremner et al 1997).
- ◆ Can CRF-overexpression model aspects of this specific CRF pathology?

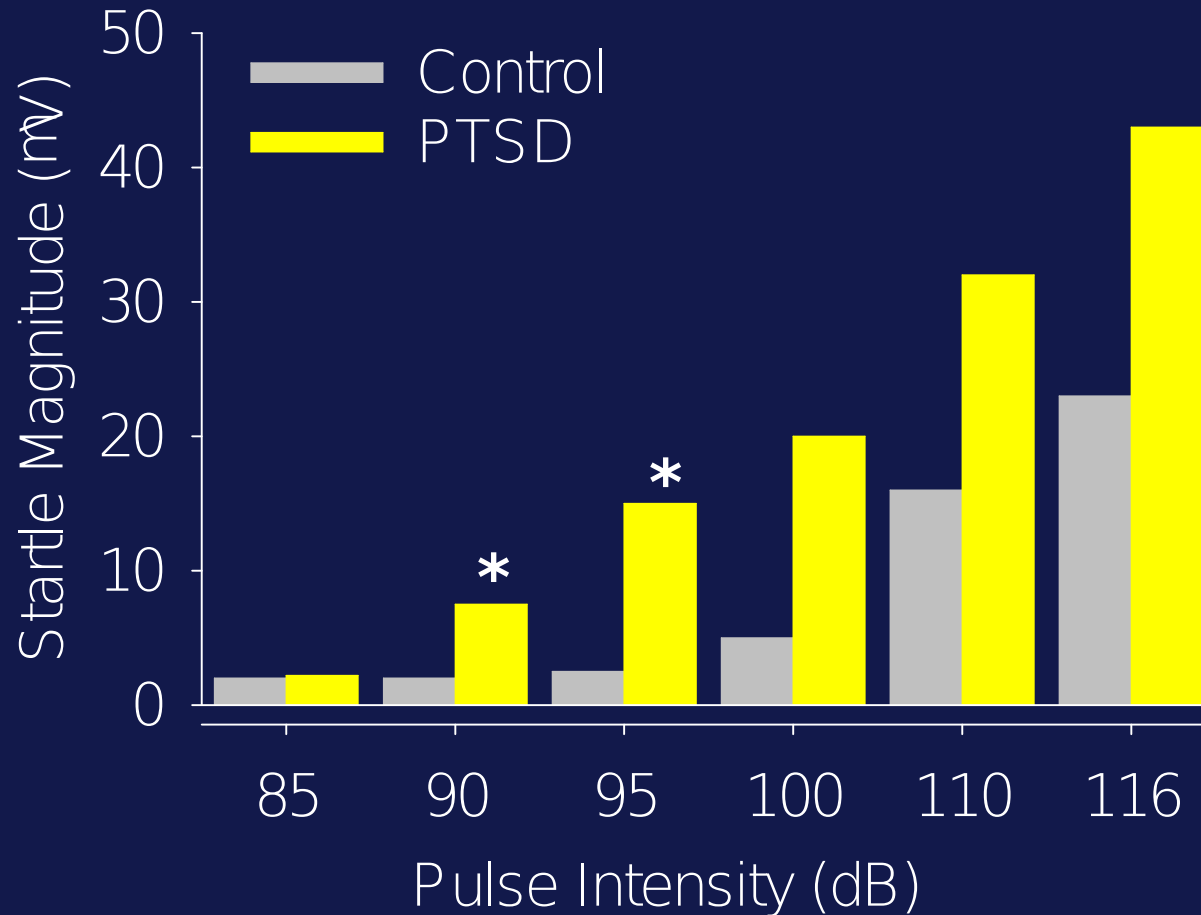


Neuronal CRF-overexpression induces increased startle reactivity in mice



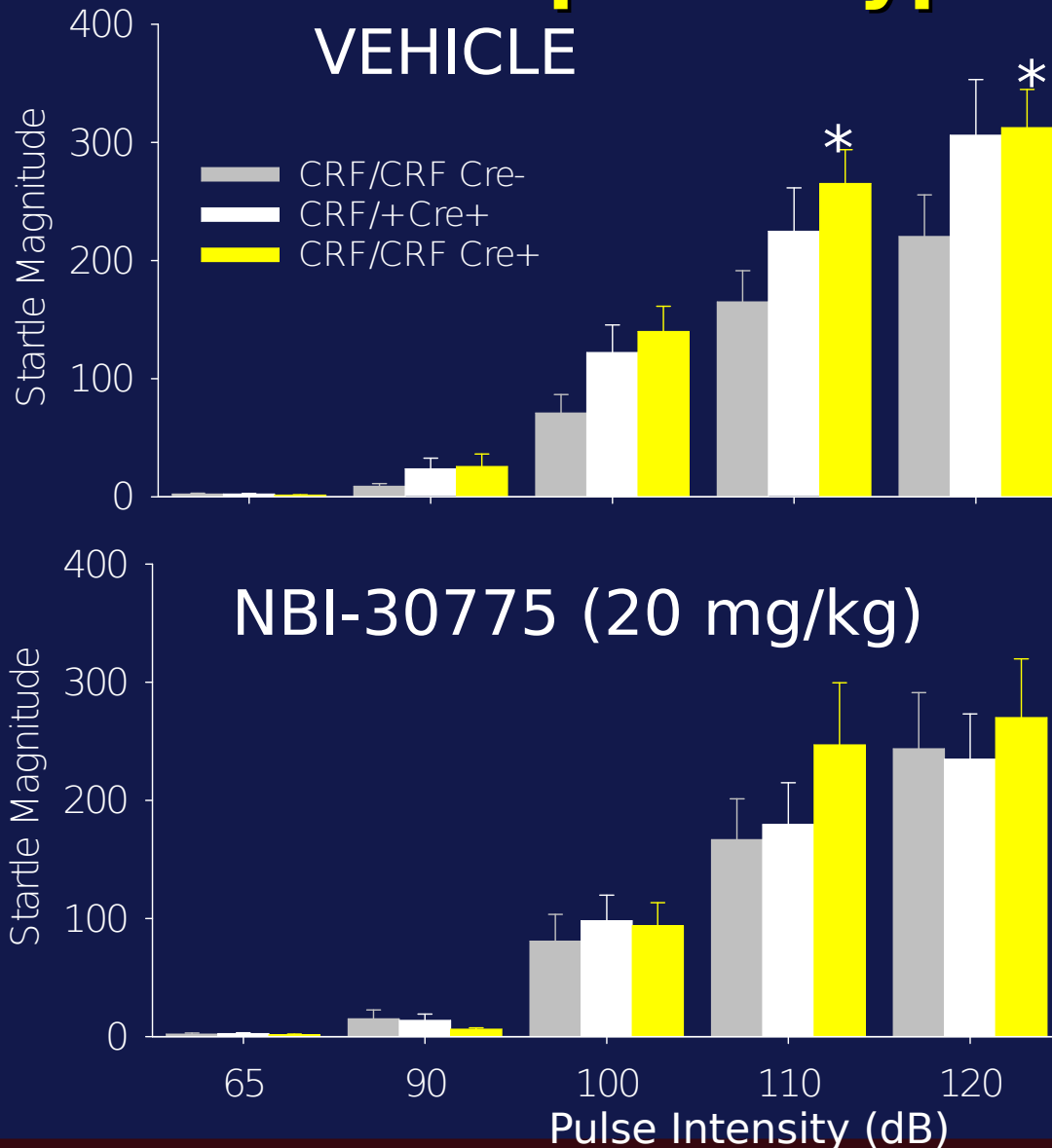
* $p < 0.05$ vs. CRF/CRF Cre-

Increased startle in PTSD



From Butler et al. 1990

CRF₁ blockade attenuates CRFOE startle phenotype



Modeling CRF contribution to trauma effects on enduring anxiety: Adamec predator stress test



10 min exposure to predator

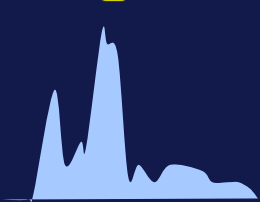
-2 days

0

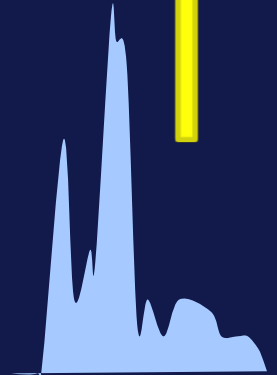
10 days



CRA0450
CRF₁ antagonist, IP



Pre-stress startle test

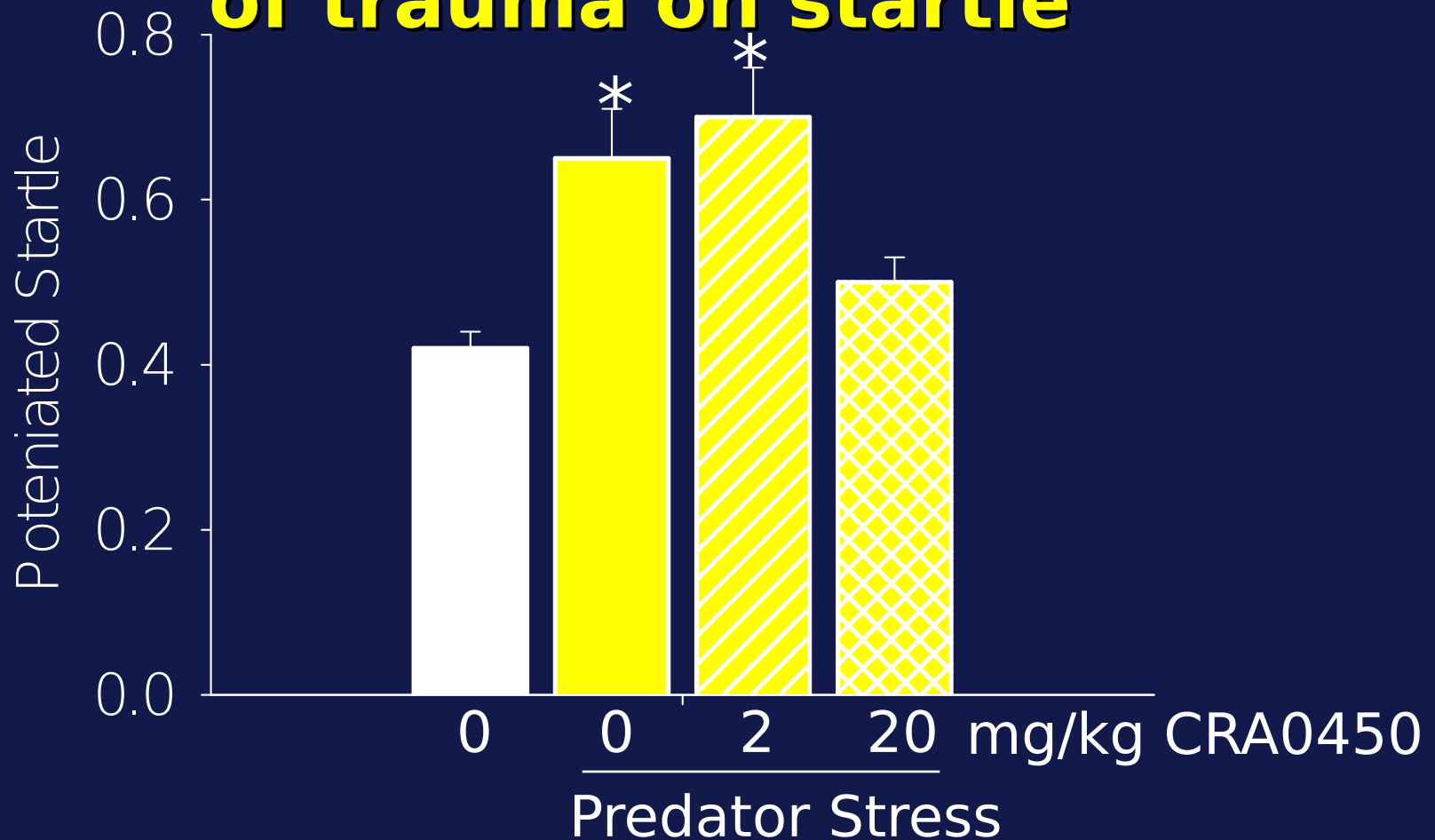


Post-stress startle test

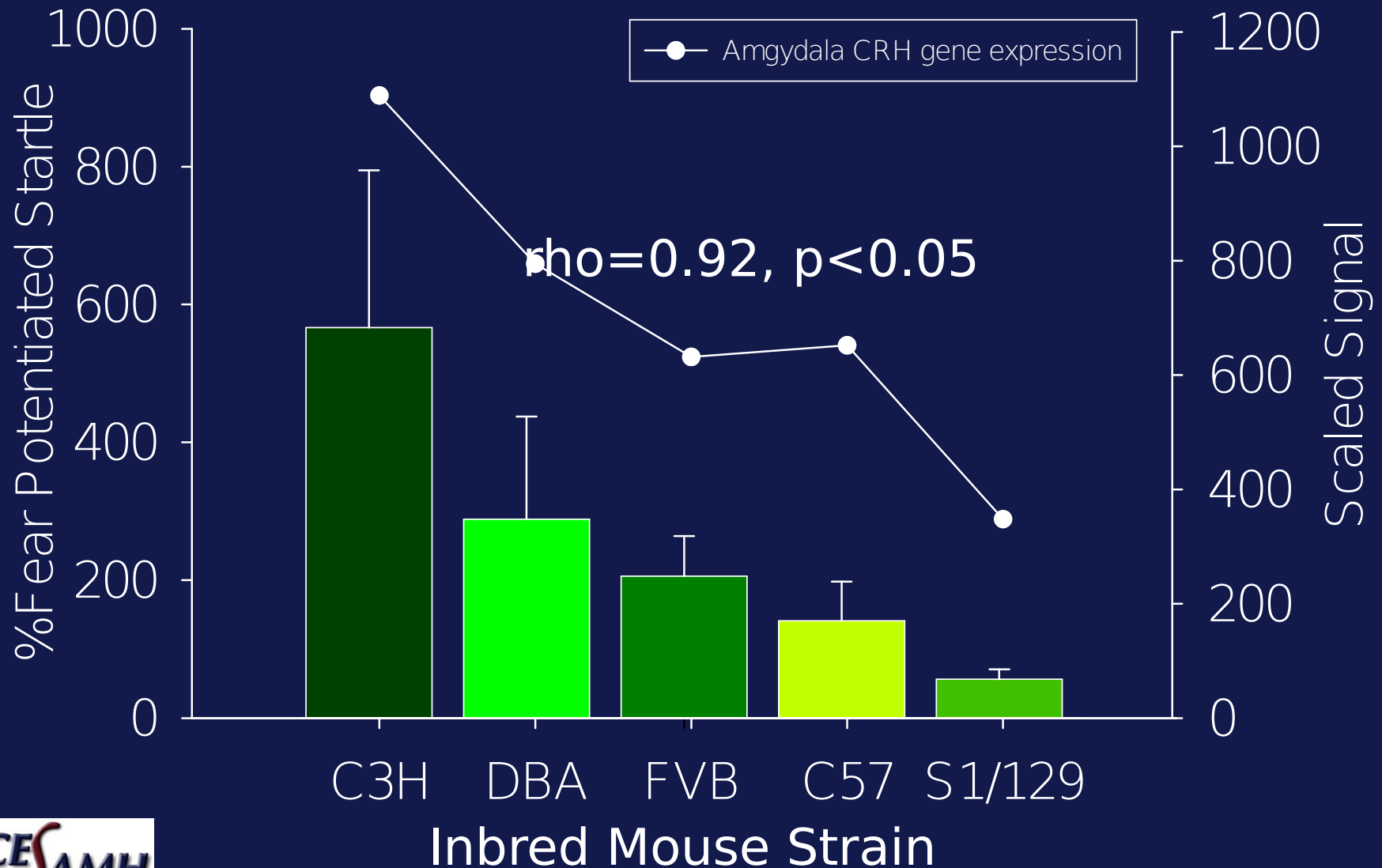


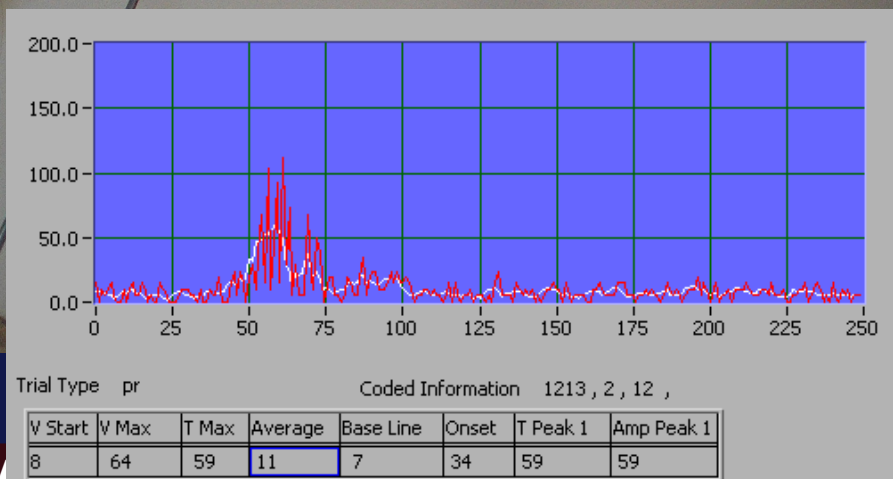
VA Center of Excellence for Stress and Mental Health

CRF₁ receptor blockade may be prophylactic against enduring effects of trauma on startle



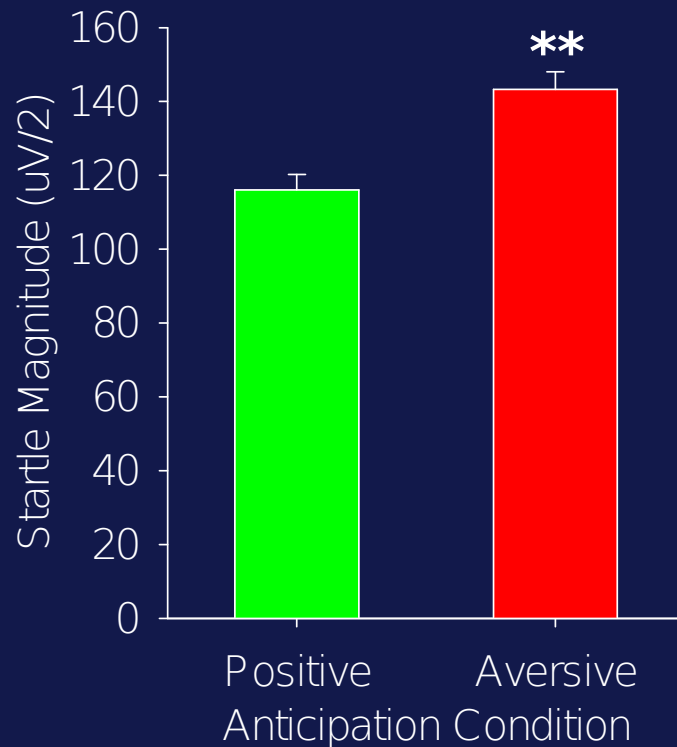
Heritable variance in CRF gene expression in amygdala predicts fear-potentiated startle





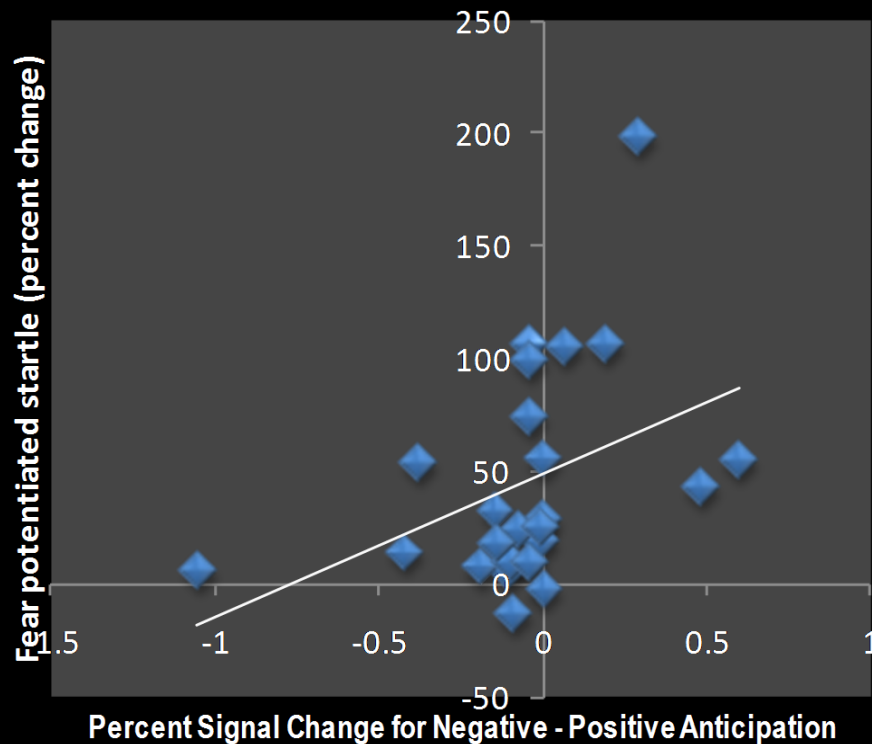
Fear Potentiated Startle

● Cue alerts subject to
oncoming stimulus - pleasant or aversive
Startle recorded during anticipation



FPS responding is linked to amygdala activation

Startle and Amygdala



Y=-5

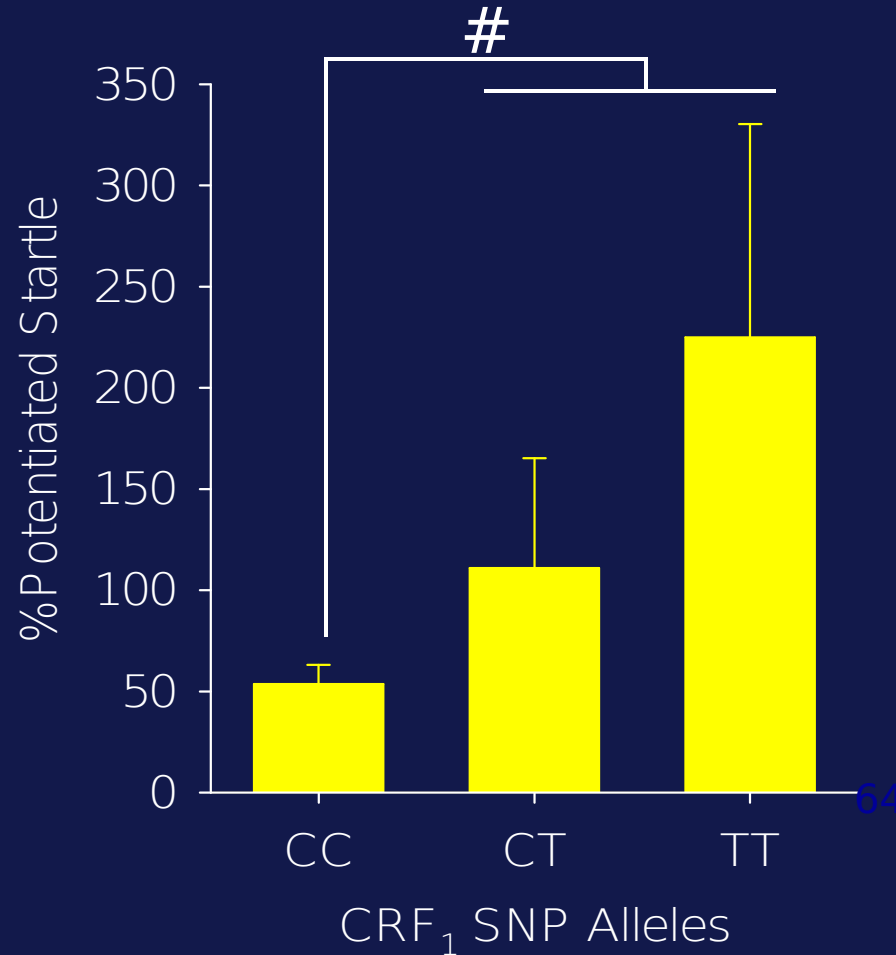


Z=-18



Robust $t=2.73$, $p<0.05$ $N=25$

FPS may be sensitive to genetic variance in CRF₁



*CRF₁ gene SNP Rs4792887 $r=.313$, $p<0.005$, $N=78$

CC vs. T carrier $t(76)=-2.5$, $p<0.008$

Examples of Translational Research in CESAMH

Neuropeptide Y

- **Basic animal model - Geyer/Risbrough lab**
- **Serial Cerebrospinal Fluid Studies of PTSD , funded by VA**
- **Marine Resiliency Study, funded by VAHSR&D, Marine Corps & Navy BUMED**
- **Goals:**
 - **To better understand the relationship between Peripheral (blood) and Central (cerebrospinal fluid) NPY concentrations and risk/resilience to combat stress**
 - **To determine the impact of NPY concentrations on physical (blood pressure) and mental health (PTSD) manifestations of stress**
 - **Using a prospective, longitudinal design, determine the impact of peripheral concentrations (blood) of NPY on risk for PTSD in Marines deployed to combat**



Summary

CESAMH resources are directed toward clinical, education and research activities

CESAMH has multiple collaborations, including with DOD

The multidisciplinary nature of the center placed the center in a unique position to do translational research

